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Prevalence of COVID infections in a population of rheumatic patients from Lombardy and Marche treated with biological drugs or small molecules: A multicentre retrospective study

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ABSTRACT

Objective: The COVID-19 pandemic has raised questions about the management of systemic immunosuppressive treatments for rheumatic conditions. It is well known that rheumatic patients are at risk of developing infections because of their immunocompromised state. Moreover, drugs such as hydroxychloroquine or tocilizumab that are widely used to treat rheumatic diseases are now being used to treat COVID-19. The aim of this multicentre retrospective study of rheumatic patients in the Italian regions of Lombardy and Marche was to determine whether patients receiving biological or small molecules treatment are more susceptible to the development of COVID-19 than the general population.

Abbreviations: WHO, World Health Organisation; MERS, Middle East respiratory syndrome; SARS, severe acute respiratory syndrome; COPD, chronic obstructive pulmonary disease; CHD, coronary heart disease; DMARDs, disease-modifying anti-rheumatic drugs; HCQ, hydroxychloroquine; CQ, chloroquine; SDAI, Simplified Disease Activity Index; DAS28, Disease Activity Score 28; DAPSA, Disease Activity Index for Psoriatic Arthritis; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index; RA, rheumatoid arthritis; HLA, human leukocyte antigen; ACR, American College of Rheumatology.

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Methods: The local registry data of 10,260 rheumatic patients being treated with bDMARDs or small molecules were evaluated from 15 March to 23 April 2020. The final analysis was based on the registry data relating to 7,204, telephone contacts and/or outpatient visits.

Results: Forty-seven of the 7,204 patients were diagnosed with COVID-19, seven of whom died; the patients who had symptoms resembling those of COVID-19 but had negative swabs were considered negative for the disease. The overall infection rate was 0.65, and the crude case fatality risk (CFR) in the patients with COVID-19 was 14.9%. There was no difference in the mortality rate among the patients receiving the different individual biological drugs or small molecules.

Conclusions: Our findings suggest that the susceptibility of rheumatic patients to COVID-19 is the same as that of the general population, but confirm that age, disease duration, and the number of co-morbidities are associated with an increased risk of a severe form of the disease. It seems that immunosuppressant drugs do not effectively represent a risk factor for COVID-19.

1. Introduction

In December 2019, the novel coronavirus later named SARS-CoV-2 by the World Health Organisation (WHO) was isolated in Wuhan, China. The virus spread rapidly throughout the world and, as of 29 April 2020, there were 3,125,267 confirmed cases of COVID-19, and 217,212 disease-related deaths.

Like other coronavirus diseases such as the Middle East respiratory syndrome (MERS) or severe acute respiratory syndrome (SARS), COVID-19 is a zoonosis that probably originated in bats. Host responses to such viral infections contribute to disease progression [1], and an excessive immune response can lead to tissue damage and multi-organ failure in severe cases. This may be important in immunocompromised hosts who potentially have a weaker immune response to infection [1–3], thus suggesting that immunosuppression may be a risk factor like an older age, environmental factors such as pollution and smoke, and comorbidities such as chronic obstructive pulmonary disease (COPD), coronary heart disease (CHD), hypertension and diabetes [4,5].

One still open question is whether rheumatic patients are more vulnerable to COVID-19 than the general population because rheumatic diseases are characterised by an unbalanced immune response and patients require immunosuppressive disease-modifying anti-rheumatic drugs (DMARDs) to control disease activity, both of which increase the risk of infection [6–10]. Paradoxically, increasing knowledge of SARS-CoV-2 has led to many drugs that are widely used to treat rheumatic diseases, such as hydroxychloroquine (HCQ), chloroquine (CQ), tocilizumab and baricitinib, being proposed as a means of controlling the most severe manifestations of COVID-19 [11–14]. Consequently, the susceptibility of rheumatic patients to COVID-19 and the potential risks/benefits of anti-rheumatic drugs in the treatment of COVID-19 remain unclear, although the leading scientific societies have issued recommendations to rheumatologists that include the use of low-dose glucocorticoids and the possible withdrawal of DMARDs during infectious episodes.

The aim of this multicentre retrospective study of rheumatic patients in Lombardy and Marche (two Italian regions greatly affected by COVID-19) was to investigate the impact of COVID-19 on rheumatic patients and assess the association between COVID-19 and the use of biological drugs or small molecules.

1.1. Materials and methods

1.1.1. Participants

The patients were selected from the local registries of biological drugs and small molecules. The inclusion criteria were an age of ≥ 18 years; a confirmed diagnosis of rheumatic disease, including rheumatoid arthritis (RA), axial spondyloarthritis, connective tissue disease and auto-inflammatory disease; a visit to the outpatient clinic of one of the nine Lombardy or Marche rheumatology centres participating in the study within the previous three months; disease duration of at least three months; and stable therapy (in order to minimise any confounding

related to the effect of recent treatment changes on the rate of infection). The exclusion criteria were malignancy or pregnancy in the previous six months.

The registries included 10,260 rheumatic patients, but only 7,204 were enrolled included in the final analysis because of the exclusion criteria, missing data, refusal to participate, or for the absence of biologics and small molecules treatment during COVID-19 period evaluated.

1.1.2. Data collection

The data collected from the local registries included demographic information, co-morbidities, medical history, medication, and disease activity measurements (Simplified Disease Activity Index [SDAI], Disease Activity Score 28 [DAS28], Disease Activity Index for Psoriatic Arthritis [DAPSA], Bath Ankylosing Spondylitis Disease Activity Index [BASDAI] and Systemic Lupus Erythematosus Disease Activity Index [SLEDAI]) and an analysis was made of the clinical outcomes of the cases of COVID-19 observed between 15 March and 23 April 2020 and confirmed by means of a naso/oropharyngeal swab specimen from the upper respiratory tract. All of the patients gave their consent to the use of registry data for scientific purposes, and the study protocol was approved by the Institutional Review Board of Luigi Sacco University Hospital, Milan.

1.2. Statistical analysis

The data were entered into a database (Microsoft Office Excel 2011, version 11.4.1, Microsoft, Redmond, WA, USA) and analysed using MedCalc®, version 19.0.1.0 (MedCalc Software, Mariakerke, Belgium). The categorical variables are expressed as numbers and percentages, and the comparisons between the study population as a whole and the COVID-19 patient were made using the χ^2 or Fisher's exact test. P values of <0.05 were considered statistically significant.

2. Results

The total population in the registries consisted of 10,260 adults (3,549 men and 6,711 women) with RA ($n = 5,373$), axial spondyloarthritis ($n = 3,283$), connective tissue disease/vasculitis ($n = 1,517$) or auto-inflammatory disease ($n = 87$) (Table 1a). Table 1b shows clinical and demographic characteristics of the patients included in the study ($n = 7,204$) and those of the 47 patients with confirmed COVID-19 (17 men and 30 women; mean age 60.6 ± 15.9 years; 48.9% with RA, 38.3% with axial spondyloarthritis, 8.5% with connective tissue disease, and 4.2% with auto-inflammatory disease).

All of the COVID-19 patients had a history of 13,25 (SD 9,43) years of disease duration with moderate/high disease activity in 72.3%. The most frequent co-morbidities were hypertension (14 patients, 29.7%) and lung diseases (10 patients, 21.2%); the co-morbidity data were not different in the rheumatic patients without COVID-19. Of the 47 subjects, 16 (34%) reported 2 medical comorbidities and 16 (31.9%)

Table 1a

Demographic and disease characteristics of the patients included in the registries (n=10260).

CHARACTERISTICS	Total patients(n = 10.260)		COVID-19 positive patients(n = 47)	
	(n°)	(%)	(n°)	(%)
Sex				
• Male	3.549	34.5	17	36.1
• Female	6.711	65.4	30	63.8
Age (years)				
• 18-35	1.179	11.4	3	6.3
• 36-59	4.654	45.3	19	40.4
• 60-75	2.721	26.5	15	31.9
• >75	1.706	16.6	10	21.2
Disease				
• Rheumatoid arthritis	5.373	52.3	23	48.9
• Axial spondyloarthritis	3.283	32	18	38.3
• Autoimmune diseases/vasculitis	1.517	14.7	4	8.5
• Autoinflammatory diseases	87	0.85	2	4.26

Table 1b

Demographic and disease characteristics of the patients included in the study (n= 7204).

	Patients in treatment with bDMARDs/small molecules		COVID-19 positive patients	
	(n°)	(%)	(n°)	(%)
	7.204	70.2	47	0.65%
Disease activity				
• Remission/low activity	2.219	30.8	13	27.7
• Moderate/high Activity	4.985	69.2	34	72.3
Drugs				
• Adalimumab	1518	21.0	12	25.5
• Infliximab	405	5.6	5	10.6
• Golimumab	532	7.3	3	6.3
• Certolizumab	371	5.1	3	6.3
• Etanercept	1243	17.2	10	21.2
• Tofacitinib	186	2.5	2	4.2
• Baricitinib	288	4.2	0	0.00
• Tocilizumab	546	7.5	1	2.1
• Sarilumab	82	1.1	0	0.00
• Anakinra	68	0.9	1	2.1
• Canakinumab	124	1.7	0	0.00
• Abatacept	800	11.1	3	6.3
• Sekukinumab	361	5.0	3	6.3
• Ustekinumab	118	1.6	0	0.0
• Ixekizumab	29	0.4	0	0.0
• Apremilast	147	2.0	0	0.0
• Belimumab	61	0.8	2	4.26
• Rituximab	325	4.5	2	4.26

Table 2

Baseline characteristics and prognosis of the 47 patients with SARS-CoV-2 infection.

CHARACTERISTICS	COVID-19 positive patients (n = 47)	
	Total number	%
Comorbidities		
• Lung diseases (includes ILD, COPD, Asthma, other lung diseases)	10	21.27
• Diabetes	4	8.52
• Hypertension	14	29.78
• Cardiovascular disease	9	19.15
• Others	4	8.52
• None	6	12.76
Prognosis		
• Hospitalization	14	29.78
• Quarantine-discharge	26	55.32
• Death	7	14.90

reported 3 or more comorbidities (Table 2).

All of the COVID-19 patients were taking bDMARDs, or small molecules, which were temporarily withdrawn during the period of active infection without giving rise to flare-ups in their rheumatic disease. Fourteen patients (29,7%) required hospitalization and seven died (Table 2) (five women and two men; mean age 69 years (SD 12,2) (range 39–78 years)). Intriguingly, five of the deceased were in rheumatic disease remission and two had moderate disease activity. Five patients were being treated with anti-TNF α drugs, one with rituximab, and one with tofacitinib. None were smokers and three had an associated cardiovascular disease.

There was no statistically significant difference between the two groups in terms of bDMARD or systemic corticosteroid treatment; 40% of the patients in both groups were receiving monotherapy.

The overall infection rate was 0.65, and the crude case fatality risk (CFR) in the patients with COVID-19 was 14.9%. There was no difference in the mortality rate among the patients receiving the different individual biological drugs or small molecules, but there was an albeit non-significant trend towards more infections among the patients receiving tumour necrosis factor inhibitors.

3. Discussion

The seriousness of the SARS-CoV-2 outbreak requires urgent multi-disciplinary action to contain the spread of the disease and prevent its complications. No vaccine is currently available and only supportive treatment is possible; it is also necessary to stratify the risk of the population in order to implement possible preventive strategies and potentially spare vulnerable people.

The recognised risk factors for a poor outcome are an advanced age, smoking, male sex, and co-morbidities such as hypertension, diabetes or pre-existing lung diseases, and immunosuppression. The susceptibility of rheumatic patients to COVID-19 is unclear because of the scarcity of epidemiological data [15]. However, it is known that rheumatic patients may be susceptible to infections due to their immunosuppressive treatments or underlying condition, and that a number of currently used anti-rheumatic medications are being tested in trials aimed at establishing their effect on SARS-CoV-2 infection. The main concern of rheumatologists is whether these medications are a potential risk or play a protective role against COVID-19 [16].

The aim of this retrospective study of 10.260 rheumatic patients in Lombardy and Marche (two of the most highly affected regions in Italy: <https://coronavirus.jhu.edu/map.html>) was to assess their susceptibility to COVID-19 and the overall effects of anti-rheumatic drugs. To the best of our knowledge, this is the largest study of SARS-CoV-2 infection in rheumatic patients.

The infection rate or incident rate (probability or risk of an infection in a population; it measures the frequency of occurrence of new instances of infection within a population during a specific time period) observed was 0.65%.

72.3% of the patients with COVID-19 had moderately/highly active rheumatic disease and this is in line with the findings of Au et al. in their large cohort of rheumatoid arthritis patients [17]. They found that greater disease activity was associated with a higher probability of developing infections, and that the rate of particularly respiratory tract infections was increased in outpatients taking TNF inhibitors. Our findings also seem to show that anti-TNF α drugs may have a less protective effect, however, further studies are needed to confirm this data.

The overall COVID-19 infection rate in our rheumatic patients treated with bDMARDs or small molecules was 0.65, and the crude case fatality risk (CFR) in the COVID-19 patients was 14.9%; this is not statistically different from the Lombardy COVID-19 surveillance data for the same period (11.377 deaths for a crude CFR of 18.3%) (p = 0.076). Lombardy has become one of the areas with the highest incidence of COVID-19. Differences in regional health policies make it difficult to compare the numbers of cases and deaths by region, but it is striking that

the CFR (conventionally expressed as the percentage of deaths due to a certain disease compared with the total number of people diagnosed with the disease for a certain period of time) in Lombardy during our observation was approximately once and a half times higher than that in Marche (12.8%) [18], and almost double that in the rest of Italy (10.8%) [19]. Moreover, as of 15 April 2020, 37% of the country's cases of COVID-19 and 53% of the deaths occurred in Lombardy, despite the fact that its 10.08 million inhabitants accounts for only one-sixth of the Italian population [18].

Our findings suggest that rheumatic patients are not more susceptible to COVID-19 than the general population, and are in line with those of Hui et al. concerning outbreaks of SARS and MERS and confirmed by D'Antiga in transplanted patients [3]. In addition, there may be a role for major histocompatibility complex human leukocyte antigen (HLA) loci in genetic susceptibility to infectious diseases. She et al. have suggested investigating whether specific HLA loci are associated with the development of anti-SARS-CoV-2 immunity and, if so, identifying the alleles related to the induction of protective immunity [8]. Given the close association between various HLA haplotypes and a number of rheumatic diseases, it would be interesting to assess whether there is an association between rheumatic diseases and SARS-CoV-2-infection related alleles.

Although it has been found that immunosuppressants are effective against COVID-19 *in vitro* and in animal models, there is currently no evidence that shows whether DMARDs protect against or induce COVID-19, and there are no studies of their potential effects on frequent users such as rheumatic patients [20]: therefore, it is still unclear whether DMARDs should be preventively withdrawn, given prophylactically, or used only in the severe stages of infection. The American College of Rheumatology (ACR) has recently suggested continuing the use of immune modifiers unless the disease is confirmed [21]. In line with these recommendations and our previous findings [16], we withdrew immunosuppressive therapy in our patients with confirmed COVID-19 and have not observed any rheumatic disease flares. Immunosuppressive therapy was resumed after patients have undergone two negative swab and their laboratory data (e.g. full blood counts, creatinine, bilirubin, albumin, LDH, AST/ALT, CK, CRP, IL-6, troponin T ferritin prothrombin (INR) and lipid profiles) have normalized. Important scientific questions have been raised about use of chloroquine and hydroxychloroquine for the treatment and prophylaxis of COVID-19. Some societies, supported by scientific background [20,22,23], such as the Indian Medical Research Council has recommended the prophylactic use of hydroxychloroquine against COVID-19 in healthcare workers and their asymptomatic contacts [22]. Recently a large multinational real-world analysis postulated that not only any benefit of hydroxychloroquine or chloroquine in COVID-19 where observed but even their use was related to an increased hazard for clinically significant occurrence of ventricular arrhythmias and increased mortality risk [24]. Therefore, World Health Organisation (WHO) has been suspending the authorization to use hydroxychloroquine and chloroquine for the treatment of COVID-19 outside clinical trials. On 3 June, three of the authors of the study have retracted it for their inability to complete an independent audit on the data supporting their analysis [25] and WHO reported the resumption of trials with hydroxychloroquine. We herein cannot express any opinion concerning the effect of hydroxychloroquine because only a few of our patients were taking it; however, in the absence of randomised clinical trials, we discourage its prophylactic use.

As a general principle, the repurposing of existing drugs with proven safety and toxicology profiles has been of great advantage during this *pandemia* in terms of buying time in the process of identifying a specific treatment for COVID-19 [26]. However, since specific drugs are still not available, it is important to find the optimal use of these repurposed drugs, including bDMARDs, which since lately have been strictly under the aegis of rheumatologists (e.g., sarilumab, tocilizumab and canakinumab). Studies about COVID-19 clinical course suggest us that these drugs can be probably used at different timings of the disease, in order to

prevent clinical deterioration and reduce the mortality rate. Conversely, the use of these drugs for prophylaxis and prevention of COVID-19 is still a matter of debate. Our findings suggest that there is neither an increased or a reduced susceptibility of COVID-19 in rheumatic patients treated with biologics or small-molecules: therefore, for now, we can rely just on patient surveillance and the endorsement of extensive preventive barrier measures.

Patient and public involvement

Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication

Not required.

4. Authorship contributions

FS SF PSP DM contribute to analysis and interpretation of the data, PSP and FS contributed to the design of the project. DM, PSP and VG wrote the manuscript. All Authors contribute to the collection of the data, and review of the manuscript. MG contribute to review of the manuscript.

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Declaration of competing interest

None declared.

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